**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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| In re application of | Docket No: Q116808 |
| Takamasa WATANABE, et al. | |
| U.S. Patent Appln. No.: 10/568,761 | Group Art Unit: 1644 |
| Confirmation No.: 6669 | Examiner: HADDAD, MAHER M |
| Filed: February 21, 2006 | |

For: PREVENTIVE OR REMEDY FOR INFLAMMATORY BOWEL DISEASES CONTAINING ANTI-CD81 ANTIBODY AS THE ACTIVE INGREDIENT

**APPEAL BRIEF UNDER 37 C.F.R. § 41.37**

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

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## I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, DAINIPPON SUMITOMO PHARMA CO., LTD. (having a business address of 6-8, Dosho-machi 2-chome, Chuo-ku, Osaka-shi Osaka, Japan), by virtue of an Assignment recorded on February 21, 2006, at Reel: 017600, Frame: 0068.

## II. RELATED APPEALS AND INTERFERENCES

To the knowledge and belief of Appellant, the Assignee, and the Appellant's legal representative, there are no other appeals or interferences before the Board of Appeals and Interferences that will directly affect or be affected by the Board's decision in the instant Appeal.

## III. STATUS OF CLAIMS

Claims 1-18 and 21-30 are canceled. Claims 19, 20 and 31-37 are pending in the Application. Claims 19, 20 and 31-37 are rejected. Rejected Claims 19, 20 and 31-37 are the subject of this Appeal.

## IV. STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final Office Action of July 1, 2011.

The Appendix included with this Brief sets forth the claims involved in the appeal and reflects all of the claim amendments that have been entered by the Examiner.

## V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Appellants' claimed invention, as recited in, for example, Claim 19, is related to the treatment of inflammatory bowel disease (IBD) in a patient, by administering to the patient a therapeutic agent that comprises an anti-CD-81 antibody. This invention is based, in part, on Appellants' discovery that the expression of CD81 is specifically increased in IBD-pathogenic cells vis-à-vis non-IBD-pathogenic cells (page 10, lines 8-12). In addition, Appellants have discovered that the administration of an anti-CD81 antibody to subjects with IBD produces an efficacious therapeutic result (page 102, lines 1-4).

**Claim 19**

A method for improving or treating inflammatory bowel disease (IBD) (page 1, lines 6-7), comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody (page 8, lines 5-10) to a patient in need thereof.

**Claim 20**

The method according to claim 19, wherein the anti-CD81 antibody (page 8, lines 5-10) is a monoclonal antibody (page 14, line 14).

**Claim 31**

The method of claim 19, in which the antibody is provided in the form of a Fab, $F(ab')_2$, Fv or single-chain Fv (page 48, lines 8-10).

**Claim 32**

The method of claim 19, wherein the patient in need thereof is suffering from IBD associated with shortening of the intestinal length (page 101, line 21-24) and wherein the shortened intestinal length is improved or treated by the method (page 102, lines 1-4).

**Claim 33**

The method of claim 19 wherein the effective amount is 0.0001 mg to 1000 mg per kilogram of the body weight of the patient for one administration (page 60, lines 2-4).

**Claim 34**

The method of claim 19 wherein the effective amount is several milligrams to 2 g per day (page 58, lines 11-13).

**Claim 35**

The method of claim 19, wherein the patient in need thereof is suffering from IBD associated with loose stool or diarrhea (page 101, lines 7-8) and wherein the loose stool or diarrhea is improved or treated by the method (page 102, lines 1-4).

**Claim 36**

A method for improving or treating inflammatory bowel disease (IBD) associated with shortening of intestinal length (page 101, line 21-24), comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody (page 8, lines 5-10) to a patient in need thereof.

**Claim 37**

A method for improving or treating inflammatory bowel disease (IBD) associated with loose stool or diarrhea (page 101, lines 7-8), comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody (page 8, lines 5-10) to a patient in need thereof.

Although the above Summary refers to specific portions of the specification, these references are not intended to be limiting in nature, but rather, are examples from the exemplary embodiments of the invention.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed, including the statute applied, the claims subject to each rejection and the references relied upon by the Examiner, are as follows:

**1.** The rejection of Claims 19, 20, 32 and 35-37 under 35 U.S.C. § 102(b) as allegedly being anticipated by Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647);

**2.** The rejection of Claims 19, 20, 31, 32 and 35-37 under 35 U.S.C. § 102(b) as allegedly being anticipated by Curd *et al.* (WO 00/67796);

**3.** The rejection of Claims 31, 33 and 34 under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,423,501, WO 98/25647 or WO 00/67796, in view of Owens *et al.*;

**4.** The rejection of Claims 19, 20 and 31-37 under 35 U.S.C. 103(a) as allegedly being obvious over Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647) in view of He (*World J. Gastroenterol.*, 2004, 10(3):309-318);

**5.** The rejection of Claims 19, 20 and 31-37 under 35 U.S.C. § 103(a) as allegedly being obvious over Fleming *et al.* (either of U.S. Patent No. 6,423,501, WO 98/25647 or U.S. Patent No. 7,026,283) in view of Stoyanova *et al.* (*Acta Histochem*, 2002, 104(2):185-192);

**6.** The rejection of Claims 19, 20 and 31-37 under 35 U.S.C. § 103(a) as allegedly being obvious over Curd *et al.* (WO 00/67796); and

**7.** The rejection of Claim 31 under 35 U.S.C. § 103(a) as allegedly being obvious over Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647) in view of Owens *et al.*

## VII. ARGUMENT

### I. Rejection of Claims 19, 20, 31, 32 and 35-37 Under 35 U.S.C. § 102(b)

**1.** Claims 19, 20, 32 and 35-37 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647). With respect to Fleming *et al.*, it is the Examiner's position that Fleming *et al.* discloses a method for treating inflammatory bowel disease, comprising administering an anti-CD81 antibody to a patient in need thereof. To make the rejection, the Examiner cites to column 13, lines 34-45, to allege that Fleming *et al.* discloses the treatment of inflammatory bowel disease, and to column 9, line 65, through column 10, line 3, as allegedly disclosing anti-CD81 antibodies.

**2.** Claims 19, 20, 31, 32 and 35-37 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Curd *et al.* (WO 00/67796). With respect to Curd *et al.*, it is the Examiner's position that Curd *et al.* discloses a method for treating inflammatory bowel disease, comprising administering an anti-CD81 antibody, citing to Claims 1, 2, 3, 6 and 7.

Appellant respectfully submits, however, that these anticipation rejections constitute reversible error because a person of ordinary skill in the art would not have "at once envisaged" the presently claimed invention from either Fleming *et al.* or Curd *et al.*, and because the anticipation rejections rely upon an excessive picking and choosing amongst different combinations of elements, which is proscribed by law.

**The Claimed Invention is Not Anticipated Because a Person of Ordinary Skill in the Art Would not Have "at Once Envisaged" the Claimed Invention from Fleming *et al.* or Curd *et al.***

Anticipation requires, in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *See Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co.*, 730 F.2d 1452 (Fed. Cir. 1984) (citing *Connell v. Sears, Roebuck*

*and Co.*, 722 F.2d 1542 (Fed. Cir. 1983). *See also*, *Net MoneyIn, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008) (In order to anticipate a claim under 35 U.S.C. § 102, a reference must disclose within the four corners of the document not only all of the elements claimed but also all of the elements arranged or combined in the same way as recited in the claim). Anticipation also requires, however, that a person of ordinary skill in the art would have "at once envisaged" the claimed subject matter from the reference. *See In re Petering*, 301 F.2d 676 (C.C.P.A. 1962).

In contending that Fleming *et al.* and Curd *et al.* anticipate the claimed invention, the Examiner is unable to point to any disclosure in either reference that suggests a direct, necessary, or single-embodiment relationship between an anti-CD81 antibody, and the treatment of inflammatory bowel disease. Rather, with Fleming *et al.*, one must specifically select inflammatory bowel disease from the myriad of inflammatory diseases recited in column 13, lines 34-45, and then specifically select an antibody from the different agents recited in column 9, line 65, to column 10, line 3. Similarly, with Curd *et al.*, one must specifically select CD81 from the myriad of B-cell surface antigens recited in Claim 2, and then specifically select inflammatory bowel disease from the myriad of diseases recited in Claim 6. That is, at no point does Curd *et al.* or Fleming *et al.* disclose the treatment of inflammatory bowel disease with an anti-CD81 antibody in a way that would be "at once envisaged" by a person of ordinary skill in the art. *See e.g., Ex parte Weikard*, Appeal No. 2010-008832 (Bd. Pat. App. & Inter. 2011; *nonprecedential*), stating that:

> [g]iven the large number of potential components, and the Examiner's inability to point to some teaching …, such as an example, claim, or similar disclosure, that suggests a direct, necessary, or single embodiment relationship between the components recited in Appellants' claim 12, we are not persuaded that an ordinary artisan … would have 'at once envisage[d]' the combination of elements required by Appellants' claim 12 … we agree with Appellants that the anticipation rejection relies on the excessive picking and choosing proscribed by *Net MoneyIN v. VeriSign* …

In just the relied-upon portions of Fleming *et al.*, at least twenty different inflammatory diseases, and several different types of agents, are disclosed. Similarly, in the relied-upon portions of Curd *et al.*, 25 different B-cell antigens are listed (Claim 2), and at least 60 different diseases are recited (Claim 6). Neither reference, however, suggests a direct, necessary, or single-embodiment relationship between an anti-CD81 antibody, and the treatment of inflammatory bowel disease, that would have led a person of ordinary skill in the art to have "at once envisaged" the claimed method. *See In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962). For example, unlike the art at issue in *Petering* and *In re Schaumann*, 572 F.2d 312 (C.C.P.A. 1978), which disclosed "specific preferences" which served to narrow the broad disclosures to just a small number of species, neither Curd *et al.* nor Fleming *et al.* disclose any preference for the treatment of inflammatory bowel disease. Furthermore, Curd *et al.* also discloses a preference for an antagonist of CD19 or CD20, not an antagonist of CD81. *See, e.g.*, Claims 4 and 5 of Curd *et al.* Appellants respectfully submit that the Examiner has reversibly erred in finding that a person of ordinary skill in the art would have "at once envisaged" the claimed subject matter from Curd *et al.* and Fleming *et al.*

**The Claimed Invention is Not Anticipated Because the Anticipation Rejections Rely Upon Excessive Picking and Choosing**

The Examiner has also committed reversible error through the excessive picking and choosing between alternative and distinct embodiments within Curd *et al.* and Fleming *et al.*, in the absence of any direct, necessary, or single-embodiment relationship between an anti-CD81 antibody, and the treatment of inflammatory bowel disease.

For anticipation, "it is not enough that the prior art reference … includes multiple, distinct teachings that [a person of ordinary skill in the art] might somehow combine to achieve the claimed invention." *Net MoneyIn, Inc.*, 545 F.3d at 1371. Rather, anticipation requires that

the reference "must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [claimed invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference." *Id.* (quoting *In re Arkley*, 455 F.2d 586, 587 (C.C.P.A. 1972).

As noted above, with Fleming *et al.*, one must specifically select inflammatory bowel disease from the myriad of inflammatory diseases recited in column 13, lines 34-45, and then specifically select an antibody from the different agents recited in column 9, line 65, to column 10, line 3. Similarly, with Curd *et al.*, one must specifically select CD81 from the myriad of B-cell surface antigens recited in Claim 2, and then specifically select inflammatory bowel disease from the myriad of diseases recited in Claim 6. However, at no point does Fleming *et al.* or Curd *et al.* disclose each element of Appellants' claimed invention, *arranged as described in the claims*, in a single source so as to direct a person of ordinary skill in the art to the claimed invention without any need for picking and choosing amongst these alternative and distinct elements. Appellants respectfully submit that such picking and choosing between large numbers of alternative and distinct elements has no place in an anticipation rejection, and does not constitute disclosure of the claimed invention "as arranged in the claim." *Id. See also Ex parte Goldenberg*, Appeal No. 2011-002484 (Bd. Pat. App. & Inter. 2011; *nonprecedential*), stating that:

> at separate locations throughout the reference, each of the elements of the claims [is disclosed], including anti-TNFα antibody and an anti-CD20 antibody … [the reference, however] does not teach a single composition with each of the claimed elements, but requires selection of the elements from groups of disclosed compounds … [t]his picking and choosing is not consistent with an anticipation rejection.

While *Arkley* and *Goldenberg* concerned compositions, rather than methods, the reasoning is equally applicable where each element of a method must be selected by picking and choosing between alternative and distinct elements.

Appellants respectfully submit that the Examiner has also committed reversible error in maintaining the anticipation rejections on the contention that *Arkley* is inapplicable, allegedly because the relied-upon disclosures in Fleming *et al.* and Curd *et al.* are "directly related" to one another. *See* page 5, 1st paragraph, of the Office Action mailed July 1, 2011. It is the Examiner's position that "all the diseases" recited in Fleming *et al.* and Curd *et al.* are "directly related" to one another as being autoimmune diseases, and that "all the antagonists" of Curd *et al.* are "directly related" to one another as being B-cell markers. On this basis, the Examiner attempts to distinguish the present case from *Arkley* by asserting that the requisite "direct relationship" exists in Fleming *et al.* and Curd *et al.*

Appellants note, however, that the relevant "direct relationship," as expressly articulated in *Arkley*, is whether there exists a direct relationship linking together each of the elements claimed, *i.e*, there must be a direct relationship between those elements that have been selected from *different* portions of the reference (*i.e.*, CD81, inflammatory bowel disease, and an antibody), not merely between the alternatives recited within any one portion. That inflammatory bowel disease, for example, is related to the other diseases listed in the cited references (because they are all inflammatory diseases), is irrelevant.

**That CD81, Antibody, and Inflammatory Bowel Disease Are Explicitly Recited in Curd *et al.* and Fleming *et al.* Does Not Alter the Fact That The Anticipation Rejections Rely Upon Excessive Picking and Choosing**

Appellants respectfully submit that the Examiner has also committed reversible error in maintaining the anticipation rejections over Curd *et al.* and Fleming *et al.* on the theory that anticipation is proper when "the [claimed] species is clearly named, [irrespective of] how many other species are additionally named," citing M.P.E.P. § 2131.02 and *Ex parte A*, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) It is the Examiner's position in this regard that because CD81, antibody, and inflammatory bowel disease are *explicitly* recited in Curd *et al.* and Fleming *et al.*, albeit at different and distinct locations in the references, Curd *et al.* and Fleming *et al.* anticipate under this rationale. *See* the paragraph bridging pages 4 and 5 of the Office Action mailed July 1, 2011.

Appellants note, however, that the claimed invention constitutes a *combination* of elements - CD81, antibody, and inflammatory bowel disease. Thus, to the extent that *Ex parte A* is relevant, if at all, it would be Appellants' *specific combination* of elements that would constitute the "species." However, as discussed above, this specific *combination* is not explicitly named, or inherently disclosed, anywhere in Fleming *et al.* or Curd *et al.*; selecting the claimed combination of elements from Fleming *et al.* or Curd *et al.,* notwithstanding their explicit disclosure individually and at different locations in the references, requires the type of excessive picking and choosing proscribed by law, *see Arkley*, 455 F.2d at 587. That is, Appellants' claimed invention is not a "species" that is "clearly named," for such would require an express and specific disclosure of using an anti-CD81 antibody to treat inflammatory bowel disease, without any selection from any alternatives being required. This is not the case with either

Fleming *et al.* and Curd *et al.*, since as discussed above, excessive picking and choosing is required.

In view of the foregoing, Appellants respectfully request that the Board reverse these rejections.

**II. Rejection of Claims 31, 33 and 34 Under 35 U.S.C. § 103(a)**

**1.** Claims 31, 33 and 34 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,423,501, WO 98/25647 or WO 00/67796, in view of Owens *et al.*

**2.** Claim 31 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647) in view of Owens *et al.*

Appellants respectfully submit that these obviousness rejections constitute reversible error, at least inasmuch as they presuppose that Curd *et al.* and Fleming *et al.* anticipate the claims from which Claims 31, 33 and 34 depend. As discussed above, this assertion of anticipation constitutes reversible error. In any event, Appellants respectfully submit that these rejections also constitute reversible error because those of ordinary skill in the art would not have reasonably expected success in performing the presently claimed method, which is discussed in greater detail below.

In view of the foregoing, Appellants respectfully request that the Board reverse these rejections.

**III. Rejection of Claims 19, 20 and 31-37 Under 35 U.S.C. § 103(a) Over Fleming *et al.***

**1.** Claims 19, 20 and 31-37 are rejected under 35 U.S.C. 103(a) as allegedly being obvious over Fleming *et al.* (U.S. Patent No. 6,423,501 or WO 98/25647) in view of He (*World J. Gastroenterol.*, 2004, 10(3):309-318).

**2.** Claims 19, 20 and 31-37 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Fleming *et al.* (either of U.S. Patent No. 6,423,501, WO 98/25647 or U.S. Patent No. 7,026,283) in view of Stoyanova *et al.* (*Acta Histochem*, 2002, 104(2):185-192).

In these rejections, it is the Examiner's position that Fleming *et al.* suggests a method of treating inflammatory bowel disease by administering an anti-CD81 antibody to target mast cells. In addition, the Examiner cites to He as allegedly disclosing a relationship between the efficacy of current or potential inflammatory bowel disease treatments, and the inhibition of mast cell degranulation. Specifically, the Examiner refers to ketotifen (an inhibitor of mast cell degranulation), APC2059 (a mast cell tryptase inhibitor) and 5-aminosalicylic acid (the beneficial effects of which are alleged to be due, in part, to its mast cell stabilizing activity) discussed therein. The Examiner also appears to speculate that the effective treatment of IBD by corticosteroids "might also be partially associated with its action on mast cells as significantly reduced numbers of mast cells were observed in the colon throughout steroid therapy." That is, it is the Examiner's position that, in view of He, a person of ordinary skill in the art at the time of the invention would have reasonably expected success in treating inflammatory bowel disease with an anti-CD81 antibody, because they allegedly would have recognized mast cells as being a cell type participating in the pathogenesis of inflammatory bowel disease. Stoyanova *et al.* is relied upon for essentially the same proposition - that mast cell degranulation correlates with the pathogenesis of inflammatory bowel disease.

Appellants, however, respectfully submit that these rejections constitute reversible error, for the following reasons.

**The Claimed Invention Would Not Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of the Invention, Because They Would Not Have Reasonably Expected Success in Treating Inflammatory Bowel Disease With an Anti-CD81 Antibody**

Appellants respectfully submit that these obviousness rejections constitute reversible error because, given the state of the knowledge in the art at the time of the invention, a person of ordinary skill in the art at the time of the invention would not have reasonably expected success in treating inflammatory bowel disease with an anti-CD81 antibody.

Because the hypothetical person of ordinary skill in the art is presumed to have known the relevant art at the time of the invention, s*ee In re GPAC*, 57 F.3d 1573, 1579 (Fed. Cir. 1995), *see also Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986), *and see also Environmental Designs, Ltd. V. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983)., an obviousness inquiry must consider rebuttal evidence from the time of the invention that shows why persons of ordinary skill in the art would not have reasonably expected success. In this regard, Appellants respectfully submit that the disclosure of Witherden *et al.* (*J. Immunol.*, 2000, 165:1902-1909) would have been highly relevant to a person of ordinary skill in the art contemplating targeting CD81 to treat inflammatory bowel disease (and is thus evidence of the knowledge possessed by persons of ordinary skill in this field at the time of the invention), because it provides insight as to how CD81 modulates inflammation.

Appellants respectfully submit that, in light of the teachings of Witherden *et al.*, the weight of the evidence supports the finding that persons of ordinary skill in the art would not have reasonably expected success in treating inflammatory bowel disease with an anti-CD81

antibody, because they would have appreciated, and taken into consideration, the broad expression, and differential effects, of CD81 on other cell types.

Specifically, as stated by Witherden *et al.*, "CD81 … is expressed on a wide variety of tissues and cell types, including both B and T cells as well as epithelial cells, and has the capacity to associate with other cell surface proteins in a cell type-specific manner." *See* page 1902, 2nd column, 2nd paragraph, of Witherden *et al.* That is, at the time of the invention, CD81 was not recognized as being selectively expressed on mast cells, but was known to be expressed on a wide variety of different cell types, and to interact with a variety of different cell surface proteins "in a cell type-specific manner." *See* page 1902, 2nd column, 2nd paragraph, of Witherden *et al.*

More specifically, Witherden *et al.* describes that CD81 was known at the time of the invention to be expressed, *inter alia*, on B-cells and T-cells, and Witherden *et al.* demonstrates that when CD81 on T-cells is targeted with antibody, its signaling stimulates T-cell activation, resulting in enhanced production of proinflammatory cytokines, such as TNF-α and IFN-γ. *See* Figures 1 and 6B of Witherden *et al.* In contrast, however, Fleming *et al.* discloses CD81 as a *negative regulator* of mast cell degranulation, *i.e.*, that induction of CD81 signaling inhibits mast cell degranulation. In other words, while persons of ordinary skill in the art would have recognized from Fleming *et al.* that an anti-CD81 antibody to inhibit mast cells should be an antibody that induces CD81 signaling, they would also have recognized that the same antibody would activate T-cells, leading to enhanced pro-inflammatory cytokine production.

Appellants respectfully submit this dichotomy in CD81 function between different cell types is highly probative of the lack of expectation of success that those of ordinary skill in the art would have possessed in performing Appellants' claimed method. This is because persons of

ordinary skill in the art at that time recognized a pre-dominant role for pro-inflammatory cytokines, such as TNF-α, in the pathogenesis of inflammatory bowel disease, and the concomitant role of T-lymphocyte activation in the production of such pro-inflammatory cytokines in the bowel mucosa.

In other words, although persons of ordinary skill in the art may have recognized from Fleming *et al.* that targeting CD81 with antibodies may reduce mast cell activation, they would also have recognized that the same antibody would enhance production of pro-inflammatory cytokines, such as TNF-α, and would thus exacerbate inflammatory bowel disease.

For example, Neurath *et al.* (*Eur. J. Immunol*, 1997, 27:1743-1750), authored by Markus Neurath, an internationally-recognized authority on inflammatory bowel disease research, disclosed that TNF-α has a predominant pathogenic role in colitis in mice. *See* the paragraph bridging pages 1743-1744 of Neurath *et al.*; Neurath *et al.* experimentally demonstrated that macrophages in the lamina propria produced high levels of TNF-α in inflammatory bowel disease, and noted that the majority of recent colitis models had revealed that the inflammation is mediated by $CD4^+$ T-lymphocytes producing high amounts of IFN-γ and TNF-α. *See* page 1749, column 1, 2nd paragraph, of Neurath *et al.*

As additional evidence, Montfrans *et al.* (*Mediators of Inflammation*, 1998, 7:149-152) disclosed that, following analysis of numerous studies on a variety of different inflammatory bowel disease animal models, the collective conclusion is that an overactive "antigen-dependent ( $CD4^+$) T lymphocyte activation will result in a high production of pro-inflammatory cytokines within the mucosal compartment and [result] in inflammatory bowel disease." *See* page 150, column 1, 1st paragraph, of Montfrans *et al.*

That is, Montfrans *et al.* and Neurath *et al.*, the teachings of which are presumed to have been known by persons of ordinary skill in the art at the time of the invention, demonstrate a predominant role for an overactive proinflammatory T-cell response, and the resulting overproduction of TNF-α by T-lymphocytes and macrophages, in inflammatory bowel disease. These animal studies confirmed previous observations in humans, in which hyperresponsive T-lymphocytes localizing to the lamina propria in patients with inflammatory bowel disease were posited to contribute to local inflammation. *See* page 571, column 1, 2nd paragraph, of Emmrich *et al.* (*Lancet*, 1991, 338:570-571).

In sum, those of ordinary skill in the art at the time of the invention appreciated the predominant role of an overactive proinflammatory T-cell response - and the resulting TNF-α production by T-lymphocytes and macrophages - in *causing* inflammatory bowel disease (discussed above), and also appreciated that an anti-CD81 antibody that induces CD81 signaling would enhance such a response. Accordingly, they would not have possessed a reasonable expectation of success in *treating* inflammatory bowel disease by administering an anti-CD81 antibody.

Rather, in view of the state of the art in this field at the time if the invention, Appellants respectfully submit that a person of ordinary skill in the art would not have reasonably expected success without an experimental demonstration of efficacy, due to the unpredictability of the **net** effect of targeting CD81 - particularly when the art recognized that targeting CD81 can enhance proinflammatory cytokine production (such as TNF-α). Appellants have demonstrated, however, through *in vivo* experimentation disclosed in the specification as filed, that targeting CD81 is effective in treating inflammatory bowel disease, which could not have been predicted or expected from the state of the art at the time of the invention. The "reasonable expectation of

success must be founded in the prior art, not in the applicant's disclosure." (Emphasis added.) *See In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

The disclosures of He and Stoyanova *et al.*, cited by the Examiner, do not compel a different conclusion. The fact that He may disclose that selective inhibitors of mast cell degranulation may be beneficial in the treatment of inflammatory bowel disease, and that Stoyanova *et al.* may disclose a role for mast cell degranulation in inflammatory bowel disease, is irrelevant because, as noted above, a reasonable expectation of success in treating inflammatory bowel disease with an anti-CD81 antibody would not have been realized simply by a recognition that mast cell degranulation contributes to inflammatory bowel disease. Rather, as Appellants have noted, persons of ordinary skill in the art would not have reasonably expected success in treating inflammatory bowel disease with an anti-CD81 antibody because they would have appreciated the collateral (and exacerbating) effects of enhancing T-cell activation - an increase in pro-inflammatory cytokine production - when inducing CD81 signaling by antibody binding.

In view of the foregoing, Appellants respectfully request that the Board reverse these rejections.

## IV. Rejection of Claims 19, 20 and 31-37 Under 35 U.S.C. § 103(a) Over Curd *et al.*

**1.** Claims 19, 20 and 31-37 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Curd *et al.* (WO 00/67796).

In this rejection, it is the Examiner's position that Curd *et al.* suggests a method of treating inflammatory bowel disease by administering an anti-CD81 antibody to target B-cells.

Appellants, however, respectfully submit that this rejection constitutes reversible error, as follows.

**The Claimed Invention Would Not Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of the Invention, Because They Would Not Have Reasonably Expected Success in Treating Inflammatory Bowel Disease With an Anti-CD81 Antibody**

Appellants respectfully submit that this obviousness rejection constitutes reversible error because, as discussed in detail above, a person of ordinary skill in the art at the time of the invention would not have reasonably expected success in treating inflammatory bowel disease with an anti-CD81 antibody. This is because they would have appreciated the collateral (and exacerbating) effects of enhancing T-cell activation - an increase in pro-inflammatory cytokine production - when inducing CD81 signaling by antibody binding.

It is the Examiner's position, however, that any lack of expectation of success evidenced by Appellants' rebuttal evidence is inapplicable to this obviousness rejection over Curd *et al.*, because Curd *et al.* allegedly discloses "antagonists such as [an] antibody that binds [to] CD81." *See* page 13, 1st paragraph, of the Office Action mailed July 1, 2011. More specifically, the Examiner contends that Witherden *et al.* is actually consistent with the disclosure of Curd *et al.* inasmuch as "targeting CD81 on T-cells with antagonistic antibody" (which antagonistic antibody the Examiner appears to believe is disclosed by Curd *et al.*) would result in *inhibiting* production of pro-inflammatory cytokine production by T-cells.

Appellants, however, respectfully submit that maintaining the rejection on this ground constitutes reversible error.

Specifically, Appellants respectfully submit that a person of ordinary skill in the art would not have recognized the anti-CD81 antibody of Curd *et al.* to be a CD81 antagonist – an assumption on which the Examiner's argument relies. For example, on page 3 of Curd *et al.*, the

term "antagonist" is not defined in the classical sense as a receptor antagonist; rather, page 3 of Curd *et al.* describes an "antagonist antibody" as an antibody that:

> upon binding to a B cell surface marker, destroys or depletes B-cells in a mammal and/or interferes with one or more B cell functions ... such depletion may be achieved via various mechanisms such as antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC), inhibition of B-cell proliferation and/or induction of B-cell death.

That is, the term "antagonist" in Curd *et al.* is used in the context of the ultimate effect on the B-cell - *i.e.*, destruction or depletion of B-cells, not that the molecule is an antagonist *per se* of the **specific B-cell surface marker** to which the molecule binds. Appellants respectfully submit that, through impermissible hindsight, the Examiner imputes this specific characteristic to the B-cell antagonists of Curd *et al.*, when no such description or implication exists.

Indeed, Appellants submit that, given the evidence of record, it would have been far from clear to those of ordinary skill in the art at the time of the invention that a CD81 antagonist should be administered. For example, in the case of mast cells (as described by Fleming *et al.*), the ligation of CD81 (*i.e.*, the induction of CD81 signaling) reduces mast cell activation and degranulation. This is because, in mast cells, CD81 is a negative regulator (*i.e.*, when activated, it transduces an *inhibitory* signal on cell activation). In contrast, Witherden *et al.* discloses that in T-lymphocytes, ligation of CD81 activates T-cells (resulting in an enhancement in pro-inflammatory cytokine release). Because of these opposing functions of CD81 in mast cells and T-cells, it would have been entirely unclear to those of ordinary skill in the art at the time of the invention that a CD81 antagonist would reduce B-cell activation. For example, if CD81 in B-cells behaves more like CD81 in mast cells than T-lymphocytes, an antibody that ligates CD81 (*i.e.*, a CD81 "agonist"), rather than a CD81 *antagonist*, would constitute a B-cell "antagonist" as this term is used by Curd *et al.*

Thus, the selection of an antibody that is a CD81 antagonist, and then to attempt to use it to target B-cells to treat inflammatory bowel disease (knowing of the opposing roles that CD81 plays in mast cells and T-cells, with the expectation therefrom of collateral exacerbating effects), is far from merely a "*predictable* use of prior art elements according to their established functions," that the Supreme Court has noted as being indicative of obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

In view of the foregoing, Appellants respectfully request that the Board reverse this rejection.

## VIII. CONCLUSION

The statutory fee (37 C.F.R. §41.37(a) and 1.17(c)) is being remitted. The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Date: December 5, 2011

## CLAIMS APPENDIX

**CLAIMS 19, 20 and 31-37 ON APPEAL:**

**1-18. (canceled).**

**19. (previously presented):** A method for improving or treating inflammatory bowel disease (IBD) comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody to a patient in need thereof.

**20. (previously presented):** The method according to claim 19, wherein the anti-CD81 antibody is a monoclonal antibody.

**21-30. (canceled).**

**31. (previously presented):** The method of claim 19, in which the antibody is provided in the form of a Fab, $F(ab')_2$, Fv or single-chain Fv.

**32. (previously presented):** The method of claim 19, wherein the patient in need thereof is suffering from IBD associated with shortening of the intestinal length and wherein the shortened intestinal length is improved or treated by the method.

**33. (previously presented):** The method of claim 19 wherein the effective amount is 0.0001 mg to 1000 mg per kilogram of the body weight of the patient for one administration.

**34. (previously presented):** The method of claim 19 wherein the effective amount is several milligrams to 2 g per day.

**35. (previously presented):** The method of claim 19, wherein the patient in need thereof is suffering from IBD associated with loose stool or diarrhea and wherein the loose stool or diarrhea is improved or treated by the method.

**36. (previously presented):** A method for improving or treating inflammatory bowel disease (IBD) associated with shortening of intestinal length, comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody to a patient in need thereof.

**37. (previously presented):** A method for improving or treating inflammatory bowel disease (IBD) associated with loose stool or diarrhea, comprising administering a therapeutic agent comprising an effective amount of anti-CD-81 antibody to a patient in need thereof.

## EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix), submitted herewith are copies of any evidence submitted pursuant to 37 C.F.R. §§ 1.130, 1.131, or 1.132 or any other evidence entered by the Examiner and relied upon by Appellant in the appeal.

Appellant submits herewith a copy of Witherden *et al.* (*J. Immunol.*, 2000, 165:1902-1909), Neurath *et al.* (*Eur. J. Immunol*, 1997, 27:1743-1750), Montfrans *et al.* (*Mediators of Inflammation*, 1998, 7:149-152), and Emmrich *et al.* (*Lancet*, 1991, 338:570-571).

These documents were submitted during prosecution on March 16, 2011, and entered into the record by way of a Request for Continued Examination on April 1, 2011.

## RELATED PROCEEDINGS APPENDIX

Submitted herewith are copies of decisions rendered by a court or the Board in any proceeding identified above in Section II pursuant to 37 C.F.R. § 41.37(c)(1)(ii).

None